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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/459,573	12/13/1999	VITALIY ARKADIEVICH LIVSHITS	0010-1066	1340

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EXAMINER

STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	22

DATE MAILED: 01/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Advisory Action</b>	<b>Application No.</b>	<b>Applicant(s)</b>
	09/459,573	LIVSHITS ET AL.
<b>Examiner</b>	<b>Art Unit</b>	
David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a)  The period for reply expires \_\_\_\_\_ months from the mailing date of the final rejection.  
b)  The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.  
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.  A Notice of Appeal was filed on 18 November 2002. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2.  The proposed amendment(s) will not be entered because:
  - (a)  they raise new issues that would require further consideration and/or search (see NOTE below);
  - (b)  they raise the issue of new matter (see Note below);
  - (c)  they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
  - (d)  they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: see *attached*.

3.  Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.

4.  Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.  The a) affidavit, b) exhibit, or c) request for reconsideration has been considered but does NOT place the application in condition for allowance because: \_\_\_\_\_.

6.  The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.  For purposes of Appeal, the proposed amendment(s) a) will not be entered or b) will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: NONE.

Claim(s) objected to: *NONE*.

Claim(s) rejected: 1-3, 7, 11-13 and 27-44.

Claim(s) withdrawn from consideration: 4-6,8-10 and 14-26.

8.  The proposed drawing correction filed on \_\_\_\_\_ is a)  approved or b)  disapproved by the Examiner.

9.  Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_.

10.  Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Status of the Application***

Claims 1-44 are pending in the application.

Claims 1-3, 7, 11-13, and 27-44 stand finally rejected.

Claims 4-6, 8-10, and 14-26 remain withdrawn from consideration as being drawn to a non-elected invention.

1. The request for reconsideration in the after final amendment of Paper No. 21, filed 12/23/02, is acknowledged. While the amendment to the claims would appear to overcome claim objections and rejection under 35 USC 112, second paragraph, the amendment does not place the claims in condition for allowance because the amendment would require further consideration of the claims and a new rejection under 35 USC 112, second paragraph. See MPEP 714.13 regarding non-entry of after final amendments.

2. A new rejection under 35 USC 112, second paragraph, would be required for the recitation of "wild strain" in line 9 of claim 45. It is unclear as to the meaning of a "wild strain" as the term is not defined by the claims or the specification. It appears that this may have been an editing error and the term is meant to be "wild-type strain". However, even if the term is meant to be "wild-type strain", it is unclear as to the scope of wild-type strains that are being compared to the claimed *Escherichia* bacterium. Furthermore, a new rejection would be required under 35 USC 112, second paragraph, in the recitation of "replacing an expression regulatory sequence" as it is unclear as to what replaces the "expression regulatory sequence" as recited in line 10 of claim 45.

3. The objection to claims 1-3 and 7 as reciting non-elected subject matter is maintained. Applicants argue the non-elected subject matter has been removed from the newly added claims. However, in view of the non-entry of the amendment, the objection is maintained for the reasons of record. It is noted that the amendment would appear to overcome this objection.

4. The rejection of claims 1-3, 7, 11-13, and 27-44 under 35 USC 112, second paragraph, is maintained. Applicants argue the newly added claims recite a standard for comparison of the expression and have corrected clerical errors. However, in view of the non-entry of the amendment, the rejection is

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maintained for the reasons of record. It is noted that the amendment would appear to overcome this rejection.

5. The scope of enablement rejection of claims 1-3, 7, 11-13, and 27-35 under 35 U.S.C. 112, first paragraph, is maintained. Applicants argue the rejection is obviated by amendment. Applicants further argue increasing protein expression by replacing the expression regulatory sequence is a well-established technique and the entire scope of the claims is now enabled. Applicants argue the claims have been amended to limit the scope of protein activities and exported amino acids. However, in view of the non- entry of the amendment, the rejection is maintained for the reasons of record. It is noted that the amendment would appear to overcome the rejection as directed to claim 47 and would not appear to overcome the rejection as directed to claims 45, 46, and 48-53. Claim 47 identifies the mechanism by which the copy number of a DNA encoding the protein is increased, i.e., a multicopy vector comprising a DNA encoding the protein. Claims 45 and 49-53 are not limited to a particular method or mechanism for increasing DNA copy number or a particular replacement expression regulatory sequence that may be used to increase protein expression. The specification does not enable the entire scope of bacteria with increased copy numbers by any method or replacing an expression regulatory sequence. Therefore, the specification does not enable the entire scope of claimed bacteria.

6. The rejection of claims 1, 2, 11-13, and 27 under 35 U.S.C. 103(a) as being unpatentable over Blattner et al. (GenBank Accession Number P75693) in view of Vrljic et al. (Mol Microbiol 22:815-826), and US Patent 6,040,160 is maintained. Applicants argue that, while Blattner et al. annotate their protein as belonging to the LysE family of export proteins, the homology of the YAHN protein of Blattner et al. to *C. glutamicum* LysE is low based on a BLAST analysis that provided a relatively low score (see page 333, right column of Vrljic et al. *J Mol Microbiol Biotechnol* 1:327-336). Applicants argue that based on the sequence annotation provided by Blattner et al., there is no reasonable expectation that the gene of Blattner et al. encodes a polypeptide that participates in amino acid excretion. It is noted that the cited reference (Vrljic et al. *J Mol Microbiol Biotechnol* 1:327-336) indicating a relatively low homology between the *Escherichia coli* YAHN polypeptide of Blattner et al. and the *C. glutamicum* LysE polypeptide was not

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available to one of ordinary skill in the art at the time of the invention and therefore, would not have been a factor in determining a reasonable expectation of success. MPEP 2143.02 states that predictability is determined at the time the invention was made. Regardless of whether the Vrljic et al. (*J Mol Microbiol Biotechnol* 1:327-336) reference was available to an ordinarily skilled artisan at the time of the invention, an absolute determination of the function of the polypeptide of Blattner et al. is not necessary for a reasonable expectation of success. As the claims are not so limited to a bacterium with an increased level of amino acid export, a reasonable expectation that the gene of Blattner et al. encodes a polypeptide that participates in amino acid excretion is not required. Instead, one of ordinary skill in the art would only need a reasonable expectation of success that overexpressing the nucleic acid of Blattner et al. would provide an increased level of the encoded protein. As written, amino acid excretion of the overexpressed protein is not a limitation of part (A) of claim 45. Even if this limitation was incorporated into the claim, the YAHN polypeptide of Blattner et al. is 100 % identical to the polypeptide of SEQ ID NO:10 (see item 12 of Paper No. 14) and would inherently exhibit amino acid export function. Thus, as stated in previous Office actions, the cited references combined with the knowledge of an ordinarily skilled artisan teach all limitations of the claims, provide a motivation for combining the references, and provide a reasonable expectation of success for practicing the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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